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(54) Title: INHIBITION OF THE ACTIVITY OF THE CAPSAICIN RECEPTOR IN THE TREATMENT OF OBESITY OR
OBESITY-RELATED DISEASES AND DISORDERS

(57) Abstract: The present invention provides a method of treating diseases or disorders benefiting from inactivating or down-
regulating the activity of the capsaicin receptor in a mammal by inhibiting the activity of the capsaicin receptor. The present invention
also provides a method of treating obesity and obesity-related diseases and disorders in a mammal by inhibiting the activity of the
capsaicin receptor.



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INHIBITION OF THE ACTIVITY OF THE CAPSAICIN RECEPTOR IN THE
TREATMENT OF OBESITY OR OBESITY-RELATED DISEASES AND DISORDERS

FIELD OF THE INVENTION

5 The present invention is in the field of human
medicine, particularly in the treatment of diseases and
disorders associated with obesity such as impaired glucose
tolerance, insulin resistance and diabetes mellitus. More
specifically, the invention relates to a method of treating
10 obesity related diseases and disorders by administering a
compound which modulates the activity of the capsaicin
receptor.

BACKGROUND OF THE INVENTION

15 Obesity and its related disorders is becoming a very
serious and world wide health problem. The prevalence of
obesity and its related disorders is increasing epidemically,
and is associated with a major reduction in the quality of
life for patients and with enormous health care cost for the
20 society¹. Prevention strategies have not only proven to
preserve the functional abilities of potential diabetics, but
also to be a national investment with the potential for a
significant return^{2,3}. Therefore, the implementation of
effective intervention strategies seems prudent⁴.

25 Obesity-induced pathology is linked with the development
of impaired glucose tolerance due to both impaired insulin
secretion and increased insulin resistance. Obesity is
associated with a cluster of disorders, such as type 2
diabetes, type 1 diabetes, cardiovascular disease,
30 hypertension, cancer, including but not limited to colon
cancer, rectal cancer, colorectal cancer, pancreatic cancer,
esophageal cancer, breast cancer, prostate cancer, uterine
cancer, kidney cancer, endometrial cancer, gall bladder

cancer, thyroid cancer, liver cancer, cervical cancer, ovarian cancer, stomach cancer, non-Hodgkin's lymphoma, multiple myeloma, and reproductive disorders, including but not limited to polycystic ovarian syndrome (PCO), infertility, and
5 impotency or erectile dysfunction. It has been shown, that by reducing the fat in the diet combined with daily exercise, the risk of developing type 2 diabetes can be reduced by 58%⁵. This improvement exceeded the gains observed after pharmacological intervention, such as with metformin. Weight loss programs
10 however, are often not successful over longer periods, and patients tend to regain weight and return to their previous bodyweight after termination of intensive monitoring. Thus, permanently reducing bodyweight, as a preventive measure for obesity-induced disorders, seems increasingly difficult.
15 Presently, only surgical modulation of the gastrointestinal tract has been proven successful for a prolonged period of time. Pharmaceutically, a reduction of bodyweight has been proven difficult; therefore the current treatment of obese patients is aimed at preventing or ameliorating their
20 complications due to obesity. The current conventional therapies are not adequate; therefore alternative ways to prevent the obesity-related disorders are needed.

SUMMARY OF THE INVENTION

25 The present invention provides a method of treating diseases or disorders benefiting from inactivating or down regulating the activity of the capsaicin receptor in a mammal by administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

30 The present invention also provides a method of treating obesity in a mammal by administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

The invention further provides a method for treating obesity-related diseases and disorders in a mammal by inactivating or down regulating the activity of the capsaicin receptor in a mammal by administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

The invention further provides a method for treating obesity-related diseases and disorders in a mammal by administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist in combination with one or more further active agents in any suitable ratios. When used in combination with one or more further active agents, the combination of compounds is preferably a synergistic combination. Synergy occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Such further active agents may be selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents and agents for the treatment of complications resulting from or associated with obesity or diabetes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a shows the 0-120 min blood glucose curves after an oral glucose tolerance test (OGTT) of 2 g/kg p.o. in 15-week old high-fat-fed male capsaicin receptor (VR1) knock-out mice and control mice, respectively.

Figure 1b shows the areas under the blood glucose curves in Figure 1a.

Figure 2 shows the group means of the plasma insulin levels 2 min after administration of glucose (2g/kg) i.p. to male VR1 knock-out mice and control mice, respectively.

5 Figure 3a and Figure 3b show the -30-120 min blood glucose curves and plasma insulin curves, respectively, after an oral glucose tolerance test (OGTT) of 2 g/kg p.o. in 21-week old Zucker obese rats. The capsaicin receptor antagonist BCTC was administered (15 mg/kg) p.o. at time -30 min, and the glucose
10 load was given at time 0.

Figure 4a and Figure 4b show the relative levels of the inflammatory markers iNOS and F4/80, respectively, in the mesenteric adipose tissue in 9 month old old Zucker obese rats
15 1 hour after they were given the capsaicin receptor antagonist BCTC (15 mg/kg) p.o. by gavage.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for treating
20 obesity or obesity related diseases or disorders in a mammal in need thereof by inactivating or down regulating the activity of the capsaicin receptor, comprising: administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

25 A further embodiment of the present invention provides a method wherein the obesity-related disease or disorder is selected from the following: type 1 diabetes, type 2 diabetes, impaired glucose tolerance, cardiovascular disease, hypertension, insulin resistance, cancer and reproductive
30 disorders.

A further embodiment of the present invention provides a method wherein the cancer is selected from: colon cancer, rectal cancer, colorectal cancer, pancreatic cancer,

esophageal cancer, breast cancer, prostate cancer, uterine cancer, kidney cancer, endometrial cancer, gall bladder cancer, thyroid cancer, liver cancer, cervical cancer, ovarian cancer, stomach cancer, non-Hodgkin's lymphoma, and multiple myeloma.

A further embodiment of the present invention provides a method wherein the reproductive disorder is selected from: polycystic ovarian syndrome (PCO), infertility, and impotency or erectile dysfunction.

A further embodiment of the present invention provides a method wherein the direct or indirect capsaicin receptor antagonist is selected from the following: natural products, synthetic organic compounds, peptides, proteins, antibodies, antibody fragments, single chain antibodies, and antibody based constructs.

A further embodiment of the present invention provides a method wherein a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist is administered in combination with a further active agent selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents, and agents for the treatment of complications resulting from or associated with obesity or obesity related diseases or disorders.

In another embodiment of the invention, an article of manufacture, or kit containing materials useful in the presently claimed methods is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for specifically inhibiting capsaicin receptor action and may have a sterile access port (for example the container may be an intravenous solution bag

or vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is a capsaicin receptor antagonist and/ or a capsaicin or anandamide neutralizing agent. The label on or associated with, the
5 container indicates that the composition is used for treating obesity and/or related disorders. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may
10 further include other materials desirable from a commercial end user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instruction to use.

A further embodiment of the present invention provides a
15 method for the treatment of conditions where low-grade inflammation is associated with obesity and obesity-related disorders, comprising: administering to a subject in need thereof, a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

20

Obesity occurs as a result of a positive energy balance when the amount of energy intake exceeds the amount of energy expenditure. Under normal conditions, excess energy is stored as fat. It is believed and to some extent known that several
25 factors from the periphery, for example leptin and insulin, are affected by this process. These factors can affect the process of food intake (and possibly of energy expenditure) and return the energy balance to neutral. This normal feed-back system of controlling energy balance is a protective
30 system that prevents obesity and its related disorders. However, mammals can easily override this feed-back system resulting in obesity-induced diseases and disorders. Obesity-induced disorders are associated with the destabilization of

other homeostatic systems, for example glucose or lipid homeostasis, eventually leading to impaired glucose tolerance associated with diminished insulin secretion and increased insulin resistance. The exact mechanisms underlying the obesity-induced disorders are not fully understood.

Obesity-induced pathologies seem to be associated with a low-grade inflammatory state⁶⁻⁸. Thus, insulin resistance and the degree of glycemic control (or HbA_{1c}) have been associated with increased levels of C reactive protein (a marker of first phase inflammation)^{9,10}. Several inflammatory markers have additionally been shown to correlate with percentage body fat in Pima Indians¹¹, thus suggesting that inflammation might have a role in the pathogenesis of obesity and its related diseases and disorders.

Several factors released or generated following tissue damage or during inflammation are capable of interacting with polymodal sensory afferent nerves. These factors include lipids, hydrogen ions, heat, ATP, serotonin, bradykinin, nerve growth factor and anandamide. They interact with various receptors (including, but not limited to, TRPV1, CB1, PG or P2X3) or ion-channels (including but not limited to ASICs (acid-sensing ion channels)) in the cell-membrane, and/or induce an alteration in the state of intracellular messengers and enzymes (including, but not limited to, ATP and PKC) provoking a cellular influx of calcium and concomitant activation of the nerve fiber. These factors can all act synergistically¹², and most often involve the capsaicin-receptor through direct or indirect activation, to provide a prompt and sufficient reaction to injury. The exogenous vanilloid, capsaicin, has been shown to selectively bind to this subset of nerve fibers via the capsaicin receptor.

Capsaicin-sensitive nerves are sensory nerve fibers that transmit afferent signals from the periphery regarding noxious

stimuli¹³, satiety¹⁴ and temperature¹⁵. The sensory afferent nerves of the A δ and C fiber types are both involved in nociception, are heat-sensitive and are able of responding to the exogenous vanilloid, capsaicin. Capsaicin has thus been
5 used as a pharmacological tool to investigate the role of these fibers.

The use of capsaicin to investigate the role of the capsaicin-sensitive nerves in laboratory mammals has been carried out for decades, especially to study their role in
10 pain. Nearly 40 years ago, capsaicin, the pungent ingredient of red hot chili pepper, was shown to selectively activate a subset of primary afferent nerves, the A δ and C fiber types. The mechanism by which this occurred was not known at that time. By administering capsaicin systemically to a mammal, an
15 acute stimulation occurs due to the influx of cations into the nerve cell, depolarization, increased excitability and the generation of action potentials. This elicits an afferent effect, as well as an efferent signal consisting of the release of vasoactive and pro-inflammatory peptides (e.g.
20 CGRP, somatostatin and Substance P). The magnitude of these signals is related to the degree of stimulation/injury underlying the interaction with the nerve fibers. The fact that stimulation of the receptor by capsaicin allows the influx of calcium makes capsaicin a neurotoxin when
25 administered at high doses. Capsaicin administered at neurotoxic doses elicits a permanent (when given to neonatal laboratory mammals) or a transient and reversible desensitization of the capsaicin-sensitive nerves (when given to adult mammals). The desensitized state permits the
30 investigation of the role of the capsaicin-sensitive nerves in normal or diseased states in laboratory mammals. The desensitized state, however does not rule out which factor is responsible for a possible change of condition. Any receptor,

ion-channel, intracellular substance or extracellular factor, with the potential to interact with the capsaicin-sensitive nerves, could theoretically be responsible for the desensitized effect - alone or in combination.

5 A number of direct capsaicin analogues have been identified (such as resiniferatoxin, RTX^{16,17} or olvanil^{18,19} and cannabinoids²⁰. Indirect activation of the capsaicin receptor can also occur for example through the activation of intracellular PKC²¹ and therefore compounds including but not
10 limited to PKC activators are considered to be indirect capsaicin agonists. Capsaicin antagonists have also been identified (such as capsazepine or ruthenium red) but have been of little functionality in *in vivo* experiments. Recently, the capsaicin receptor antagonist N-(4-tertiarybutylphenyl)-4-
15 (3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide (BCTC) has been shown effective with regard to inhibiting capsaicin-mediated hyperalgesia, inflammatory hyperalgesia or allodynia, and hyperalgesia after nerve injury^{22,23}.

20 The role of the capsaicin sensitive nerves in normal energy balance has been investigated through experimental studies using capsaicin desensitization. It was found that capsaicin sensitive nerves have an effect on food intake¹⁴, temperature regulation¹⁵ and glucose homeostasis through altered insulin secretion²⁴ and insulin sensitivity²⁵.

25 In laboratory animal models of obesity and its related disorder type 2 diabetes, we have recently shown that desensitization by means of capsaicin or RTX improves glycemic control, including blood glucose levels and HbA_{1c}^{26,27}, dyslipidemia²⁷, the activity of plasma dipeptidyl peptidase IV
30 (DPP IV)²⁸, insulin secretion²⁹ and insulin sensitivity³⁰. These findings suggest the system of capsaicin-sensitive nerves is overactive during obesity or obesity-related disorders. Down-regulation of capsaicin-sensitive nerves could be a novel

pharmacological way of treating obesity and obesity-related disorders.

It has been shown that capsaicin binds to a specific receptor, the capsaicin receptor. This receptor, also called
5 the vanilloid receptor 1 (VR1) or transient receptor channel vanilloid 1 (TRPV1), was cloned and described several years ago^{31,32}. The capsaicin receptor is found in the membrane of peripheral sensory afferent nerves and in various brain regions such as hypothalamus, hippocampus and substantia
10 nigra³³. The receptor is also found on non-neuronal cells like mast cells, keratinocytes, white blood cells, and macrophages³⁴. The endogenous ligand for the capsaicin receptor has not yet been identified, although ligands from the fatty acid and eicosonoid pools, such as anandamide, have
15 been convincingly suggested³⁵.

Two research groups have generated and characterized knock-out mice lacking the capsaicin receptor. The mice were found to be severely deficient in their responses to chemical or thermal sensitivity³⁶, and although the mice appeared normal
20 in a wide range of behavioral tests, including responses to acute noxious thermal stimuli, their ability to develop carrageenan-induced thermal hyperalgesia was completely absent³⁷. These data suggest that the capsaicin receptor is required for inflammatory sensitization to noxious thermal
25 stimuli, and that alternative mechanisms exist that are sufficient for normal sensation of noxious heat.

Glucose intolerance can be induced by a high-fat diet in normal mice and is, in early phases, solely explained by reduced glucose effectiveness, whereas insufficient early
30 insulin secretion is of importance after long-term feeding³⁸.

The present invention details the surprising discovery that in the capsaicin receptor knock-out mice, the state of impaired glucose tolerance after a period on high-fat diet was

improved in the mice lacking the capsaicin receptor, and that this was associated with a potentiated insulin response to glucose. Thus, the capsaicin receptor is involved in mediating the high-fat induced glucose intolerance partly through
5 reducing glucose-stimulated insulin secretion. Consequently, erasing, blocking or antagonizing the capsaicin receptor action ameliorates the consequences of obesity and could accordingly be used as a novel treatment for obesity and disorders related thereto.

10 Glucose tolerance can vary from hour to hour³⁹, but is generally constant in normal individuals. In obesity or obesity-related disorders, glucose intolerance, due to decreased insulin secretion or insulin sensitivity, is present. According to World Health Organization criteria,
15 glucose intolerance (IGT) is characterized by two hour plasma glucose values between 7.8 and 11.0 mM following a standard oral glucose tolerance test (OGTT).

As used herein, "treating" or "treatment" describes the management and care of a patient for the purpose of combating
20 the disease, condition, or disorder. Treating includes the administration of a compound of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. Treating impaired glucose
25 tolerance therefore includes the inhibition of rise in blood glucose following a standard oral glucose tolerance test, possibly in association with improved insulin secretion and/or insulin sensitivity.

As employed herein, the term "obesity" implies an excess
30 of adipose tissue. In this context, obesity is best viewed as any degree of excess adiposity that imparts a health risk. The distinction between normal and obese individuals can only be approximated, but the health risk imparted by obesity is

probably a continuum with increasing adiposity. However, in the context of the present invention, individuals with a Body Mass Index (BMI = body weight in kilograms divided by the square of the height in meters) above 25 are to be regarded as obese.

As used herein, the term "related disorders" includes but is not limited to type I diabetes, type 2 diabetes, cardiovascular disease, cancer, and other disease states whose etiology stems from or is associated with obesity.

The term "low-grade inflammation" as employed herein refers to a condition characterised by subtle increase of inflammatory markers to a degree that is far below that seen in acute infections. Inflammatory markers include, but are not limited to, C reactive protein, serum amyloid A protein, leucocyte count, cytokines (e.g. IL-6, IL-8 and TNF-alpha) and neuropeptides (e.g. CGRP). For further information with regard to the relationship between obesity and inflammation, reference may be made to an article by Ramos et al. in Surgery, 134(2), pp. 329-335 (2003), and references cited therein.

The term "administering" or "administration", as used herein encompasses any means for introducing a capsaicin-receptor antagonist or antibody to capsaicin or capsaicin analogues (both direct and indirect) into the body such that the substance is able to interact with the capsaicin receptor or with capsaicin or capsaicin analogues. Preferred routes of administration will introduce the substance into the systemic circulation. Examples include, but are not limited to, oral administration, as well as transdermal, subcutaneous, intravenous and intramuscular injection.

The active agents employed in the context of the present invention are administered to a mammal, preferably a human, in

accordance with known methods, such as intravenous administration as a bolus, or by continuous infusion over a period of time, or by intramuscular, intraperitoneal, intracerebral, intracerebrospinal, subcutaneous, intra-
5 articular, intrasynovial, intrathecal, intraocular, intralesional, oral, topical or pulmonary (i.e. by inhalation) administration, or via sustained release.

A "therapeutically-effective" amount is at least the minimal dose, but less than a toxic dose, of an active agent
10 which is necessary to impart therapeutic benefit to a mammal. Stated another way, a therapeutically-effective amount is an amount which induces, ameliorates or otherwise causes an improvement in the glucose intolerant state of the mammal.

"Carriers" as used herein include pharmaceutically-
15 acceptable carriers, excipients, or stabilizers which are non-toxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically-acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers
20 include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecule weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids
25 such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt forming counter ions such as sodium; and/or nonionic
30 surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

The term "combination therapy", "combined", "in combination with", and the like, as used herein refers to the

administration of a single pharmaceutical dosage formulation which comprises the a capsaicin-receptor antagonist or antibody to capsaicin or capsaicin analogue compound of the present invention and another active agent(s), as well as
5 administration of each active agent(s) in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, the compound of the present invention and another active agent(s) can be administered to the patient at essentially the same time, i.e. concurrently, or at
10 separate staggered times, i.e. sequentially. When given by different dosage formulations, the route of administration may be the same or different for each agent. Any route of administration known or contemplated for the individual agents is acceptable for the practice of the present invention.

15 The term "mammal" as used herein refers to any animal classified as a mammal, including humans, domestic farm and zoo animals, and sports or companion animals, etc. In a preferred embodiment of the invention, the mammal is a human.

The term "antibody" is used in the broadest sense and
20 specifically includes monoclonal antibodies, chimeric antibodies, humanized antibodies, and fully human antibodies.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogenous antibodies, i.e., the individual antibodies
25 comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Antibody fragments" refers to a portion of an intact antibody, preferably the antigen binding or variable region of
30 the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₁ and Fv fragments; diabodies: linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

The term "Fv" is the minimum antibody fragment which contains a complete antigen-recognition and binding site. This region consists of a dimer of one heavy- and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three complementarity-determining regions (CDRs) of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDR specific for an antigen) has the ability to recognize and bind antigen, although at a lower avidity than a complete antibody.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fv fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

Papain digestion of antibodies produces two identical antigen-binding fragments, called Fab fragments, each with a single antigen-binding site, and a residual Fc fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-combining sites and is still capable of crosslinking antigen.

The "light-chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino

acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG1, IgG2, IgG3, IgA1 and IgA2.

"Single-chain Fv" antibody fragments comprise the VH and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domain, which enables the sFv to form the desired structure for antigen binding. The term "immunoadhesion" designates antibody-like molecules that combine the binding specificity of a heterologous protein (an 'adhesion') with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesions comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e. is heterologous), and an immunoglobulin constant domain sequence in the immunoadhesion may be obtained from any immunoglobulin such as IgG-1, IgG-2, IgG-3 or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen binding sites.

A "capsaicin receptor antagonist" is any compound that partially or fully antagonizes, blocks, or otherwise inhibits the biological action of the endogenous capsaicin receptor

ligand, capsaicin or capsaicin analogues by binding to the capsaicin receptor (direct antagonist) or by blocking the activating stimulus (indirect antagonist/allosteric antagonist) without causing stimulation, e.g. influx of calcium into the cell. Examples of compounds that are receptor antagonists without agonist activity (no stimulation of calcium influx into the cell) are halogenated analogs of RTX^{43,44}), diaryl piperazines and related compounds⁴⁵, N-(3-acyloxy-2-benzylpropyl)-N'-[4-(methylsulfonylamino)benzyl]-thiourea analogues⁴⁶ KJM429 [N-(4-tert-butylbenzyl)-N'-[4-(methylsulfonylamino) benzyl] thiourea] and JYL1421 [N-(4-tertbutylbenzyl)- N'-[3-fluoro-4-(methylsulfonylamino) benzyl] thiourea]⁴⁷ N-(4- chlorobenzyl) -N'-(4-hydroxy-3-iodo-5-methoxybenzyl) thiourea (IBTU)⁴⁸, acyclic phenethylthiocarbamate derivatives⁴⁹, (urea derivatives and others⁵⁰⁻⁵², amine derivatives⁵³, pyridine derivatives⁵⁴, urea and amid derivatives ^{55,56} , BCTC^{22 23}, N-alkylglycines⁵⁷, SB-366791 (N-(3-methoxyphenyl)-4-chlorocinnamide)⁵⁸, and the like. Compounds including, but not limited to, these examples are thus consistent with various embodiments of the present invention.

Direct capsaicin receptor antagonists or indirect capsaicin receptor antagonists are compounds useful in the presently claimed method and include but are not limited to natural products, synthetic organic compounds, peptides, proteins, antibodies, antibody fragments, single chain antibodies, and antibody based constructs.

The current level of skill in the art of receptor binding and capsaicin receptor assays places capsaicin receptor antagonists well within the grasp of the ordinarily skilled artisan. There are several routine approaches for identifying a capsaicin receptor antagonist. One basic scheme involves a receptor binding assay followed by measurement of calcium

influx into the cell harboring the receptor. This is accomplished using routine radiometric binding methods. Characterization can also be performed using functional tests on cells expressing the VR1 receptor (clonal cell line or dorsal root ganglion cell) in order to evaluate whether they inhibit the cellular influx of calcium provoked by an agonist (e.g. capsaicin, low pH or elevated temperatures (>45°C)). Determination of calcium influx can be made by using fluorescent calcium dyes (e.g. FURA-2), radioactive calcium, or by patch clamp techniques. Compounds that bind or by themselves do not stimulate the cellular influx of calcium are considered as antagonists. The *in vivo* effects of such compounds may be evaluated by various pain related tests such as their ability to counteract the pain/hyperalgesia elicited by intraplantar injection of capsaicin in a rodent paw.

Cellular based assays can be used to identify indirect capsaicin receptor agonists⁵⁹ and therefore also their antagonists.

Antibody-based capsaicin-receptor antagonists are also consistent with the claimed method. Anti-capsaicin receptor antibodies may be generated by a variety of well-known methods that include traditional antisera production and monoclonal antibody techniques. Modified antibody forms described above may then be produced using established techniques. Once generated, the antibodies are checked for capsaicin receptor antagonist activity in the manner described above.

Neutralizing agents of capsaicin or its direct or indirect analogues represent other aspects of the invention. In this embodiment, capsaicin or its direct or indirect analogues are neutralized or otherwise rendered biologically inactive thereby not being able to affect the receptor. Agents suitable for this application are those which specifically bind capsaicin or its direct or indirect analogues, preferably

with a higher affinity constant than that of the capsaicin receptor.

Antibody or antibody-based agents are preferred because they can be purposefully generated using well established techniques.

Immunoadhesions (Fc fusion constructs, similar to ENBREL®, where the soluble ligand-binding domain of the capsaicin-receptor is fused to human Fc) are also consistent with this aspect of the invention.

Dosage and Formulation

A suitable direct or indirect capsaicin receptor antagonist can be administered to patients to treat obesity and other related diseases and disorders as the compound alone and or mixed with an acceptable carrier in the form of pharmaceutical formulations. Those skilled in the art of treating obesity and other related diseases and disorders can easily determine the dosage and route of administration of the compound to mammals, including humans, in need of such treatment. Dosages and desired drug concentration for pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. Animal experiments provide reliable guidance for the determination of effective doses for human therapy.

The route of administration may include but is not limited to oral, intraoral, rectal, transdermal, buccal, intranasal, pulmonary, subcutaneous, intramuscular, intradermal, sublingual, intracolonic, intraocular, intravenous, or intestinal administration. The compound is formulated according to the route of administration based on acceptable pharmacy practice (Fingl et al., in *The Pharmacological Basis of Therapeutics*, Ch. 1, p.1, 1975; *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing

Co, Easton, PA, 1990).

The pharmaceutically acceptable direct or indirect capsaicin receptor antagonist composition of the present invention can be administered in multiple dosage forms such as
5 tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, *in situ* gels, microspheres, crystalline complexes, liposomes, micro-emulsions, tinctures, suspensions, syrups, aerosol sprays and emulsions. The composition of the present
10 invention can also be administered in oral, intravenous (bolus or infusion), intraperitoneal, subcutaneous, transdermally or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. The composition may be administered alone, but generally will be administered
15 with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the composition of the present invention will, of course, vary depending upon known factors,
20 such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of
25 administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disease state.

30 By way of general guidance, the daily oral dosage of the active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per

day, and most preferably between about 0.6 to 20 mg/kg/day. Intravenously, the daily dosage of the active ingredient when used for the indicated effects will range between 0.001 ng to 100.0 ng per min/per Kg of body weight during a constant rate infusion. Such constant intravenous infusion can be preferably administered at a rate of 0.01 ng to 50 ng per mm per Kg body weight and most preferably at 0.1 ng to 10.0 mg per mm per Kg body weight. The composition of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. The composition of this invention may also be administered by a depot formulation that will allow sustained release of the drug over a period of days/weeks/months as desired.

The composition of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The composition is typically administered in a mixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, aerosol sprays generated with or without propellant and syrups, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert

carrier such as but not limited to, lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, and sorbitol; for oral administration in liquid form, the oral drug components can be
5 combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as, but not limited to, ethanol, glycerol, and water. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable
10 binders include, but not limited to, starch, gelatin, natural sugars such as, but not limited to, glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, and waxes. Lubricants used in these
15 dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, and sodium chloride. Disintegrants include, but are not limited to, starch, methyl cellulose, agar, bentonite, and xanthan gum.

The composition of the present invention may also be
20 administered in the form of mixed micellar or liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. Permeation
25 enhancers may be added to enhance drug absorption.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (i.e., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the
30 present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same.

The compositions of the present invention may also be

coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the composition of the present invention may be combined with a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 0.1 milligram to about 500 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivative, magnesium stearate, and stearic acid. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols

such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solution for parenteral administration preferably contains a water-soluble salt of the active ingredient, suitable stabilizing agents, and if
5 necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as
10 benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington: The Science and Practice of Pharmacy*, Nineteenth Edition, Mack Publishing Company, 1995, a standard reference
15 text in this field

Representative useful pharmaceutical dosage forms for administration of the compound of this invention can be illustrated as follows:

Capsules

20 A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

25

Soft Gelatin Capsules

A mixture of active ingredient in digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin
30 to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so
5 that the dosage unit, for example is 100 milligrams of active
ingredient, 0.2 milligrams of colloidal silicon dioxide, 5
milligrams of magnesium stearate, 275 milligrams of
microcrystalline cellulose, 11 milligrams of starch and 98.8
milligrams of lactose. Appropriate coatings may be applied to
10 increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by
injection may be prepared by stirring for example, 1.5% by
15 weight of active ingredient in 10% by volume propylene glycol
and water. The solution should be made isotonic with sodium
chloride and sterilized.

Suspension

20 An aqueous suspension can be prepared for oral and/or
parenteral administration so that, for example, each 5 mL
contains 100 mg of finely divided active ingredient, 20 mg of
sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g
of sorbitol solution, U.S.P., and 0.025 mL of vanillin or
25 other palatable flavoring.

Biodegradable Microparticles

A sustained-release parenteral composition suitable for
administration by injection may be prepared, for example, by
30 dissolving a suitable biodegradable polymer in a solvent,
adding to the polymer solution the active agent to be
incorporated, and removing the solvent from the matrix thereby
forming the matrix of the polymer with the active agent

distributed throughout the matrix.

All references, including publications, patent
5 applications, and patents, cited herein are hereby
incorporated by reference to the same extent as if each
reference were individually and specifically indicated to be
incorporated by reference and were set forth in its entirety
herein (to the maximum extent permitted by law).

10 Any combination of the above-described elements in all
possible variations thereof is encompassed by the invention
unless otherwise indicated herein or otherwise clearly
contradicted by context.

The use of the terms "a" and "an" and "the" and similar
15 referents in the context of describing the invention
(especially in the context of the following claims) are to be
construed to cover both the singular and the plural, unless
otherwise indicated herein or clearly contradicted by context.

The terms "comprising," "having," "including," and
20 "containing" are to be construed as open-ended terms (i.e.,
meaning "including, but not limited to,") unless otherwise
noted and should be read as encompassing the phrases
"consisting", "substantially comprised of," and "consisting
essentially of" (e.g., where a disclosure of a composition
25 "comprising" a particular ingredient is made, it should be
understood that the invention also provides an otherwise
identical composition characterized by, in relevant part,
consisting essentially of the ingredient and (independently) a
composition consisting solely of the ingredient).

30 Recitation of ranges of values herein are merely intended
to serve as a shorthand method of referring individually to
each separate value falling within the range, unless otherwise
indicated herein, and each separate value is incorporated into

the specification as if it were individually recited herein. Unless otherwise stated, all exact values provided herein are representative of corresponding approximate values (e.g., all exact exemplary values provided with respect to a particular factor or measurement can be considered to also provide a corresponding approximate measurement, modified by "about," where appropriate).

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

Preferred embodiments of this invention are described herein. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

EXAMPLES

5 The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

The capsaicin receptor (VR1) antagonist BCTC (*vide supra*)
10 employed as described below may be synthesized as described in WO 02/08221.

EXAMPLE 1

Laboratory animals: Male (n=11) capsaicin receptor (VR1) knock
15 out mice (Strain name: B6.129S4-*Trpv1*^{tm1Jul}, Stock Number: 003770) and male control mice (n=8) were purchased from Jackson Laboratories, Bar Harbor, ME, U.S. The mice were transported to Denmark at the age of 5 weeks and were kept under ambient controlled conditions on a normal day light
20 cycle (lights on at 6 am, lights off at 6 pm) at the Måløv Animal Unit at Novo Nordisk A/S, Denmark from then and until the age of 29 weeks of age. The mice were kept in groups (one group per cage) in standard cages (Eurostandard Type IV, Techniplast, Scanbur, Denmark) and were given free access to
25 acidified (0,4 % citric acid) tap water and standard chow (Altromin, Brogaarden Aps, Denmark). The cages were supplied with wooden wool (Brogaarden, Denmark) as nesting material and the bedding material was aspen chips (Brogaarden, Denmark), changed twice per week as was the bottles of acidified water.
30 At the age of 11 weeks, the chow was changed to a high fat diet (Research Diet Prod. No. D12309, Research Diet Inc, New Brunswick, U.S.).

Oral glucose tolerance test (OGTT)

After 15 weeks on the high fat diet, an OGTT was performed. The mice were fasted for 18 hours prior to the OGTT. Fasting blood glucose was determined as described below where after
5 glucose at a concentration of 500 mg/ml (Sygehus apotekerne, Denmark) was given orally by gavage (2 g/kg po). Blood samples for the determination of blood glucose were obtained from the tail tip capillary of conscious mice. Blood was collected in heparinized 5 μ l capillary tubes and immediately suspended in
10 250 μ l EBIO buffer (EBIO, Eppendorf, Germany). Following the experiment, glucose was determined using the glucose oxidase method (EBIO, Eppendorf, Germany). The area under the blood glucose curves (AUC) was determined by the trapezoidal method. The mean of the two groups were compared by use of the
15 Student's t-test method. $P < 0.05$ was considered to be a statistically significant difference.

Figure 1 shows the 0-120 min blood glucose curves (a) after an oral glucose tolerance test (OGTT) of 2 g/kg po in 15 week high fat fed male capsaicin receptor (VR1) knock-out or
20 control mice. The male control mice (triangle up) shows a marked increase in glucose levels following the oral glucose load with blood glucose levels 120 min after the glucose load still elevated above baseline (fasting blood glucose values at time 0 min) suggesting a delayed glucose clearance from the
25 blood, i.e. impaired glucose tolerance. The male VR1 knock-out mice (square) shows in comparison a diminished rise in blood glucose and a 120 min blood glucose level back to baseline (fasting blood glucose at time 0 min) thus resembling blood
30 glucose levels in a normal mouse (not on high fat diet) after an OGTT, i.e. normal glucose tolerance.

The group mean of the calculated area under the curve of the blood glucose curves (b) shows that during the test period of 120 min, the overall blood glucose levels were highly

statistically significantly decreased in the VR1 knock-out mice (filled bar) as compared to the control mice (hatched bar) and proves that glucose intolerance is significantly less pronounced in VR1 knock-out mice as compared to controls after a 15 week period of high fat diet. Down-regulation of the capsaicin receptor could thus be a pharmacological approach in the prevention and treatment of impaired glucose tolerance and its related disorders.

10 Glucose (ip) stimulated early insulin secretion

After 18 weeks on high fat diet, the insulin secretion of the mice was tested by injecting glucose intraperitoneally. The mice were fasted for 18 hours prior to the test. Glucose at a concentration of 500 mg/ml (Sygehus apotekerne, Denmark) was given intraperitoneally by injection (2 g/kg i.p.). The assessment of early insulin response to i.p. glucose was assessed 2 min after exposure by sampling app. 70 μ l blood from the tail tip capillary of conscious mice into heparinized 100 μ l capillary tubes. These tubes were spun (4000 rpm/min/ 4° C) and the 15 μ l plasma preserved and stored at - 20° C until analysis using an in house ELISA. The mean 2-min plasma insulin levels of the two groups was compared by the nonparametric Mann-Whitney U test due to a statistically significant difference between the variances of the groups. $P < 0.05$ was considered to be a statistically significant difference.

Figure 2 shows the group means of the plasma insulin levels 2 min after glucose (2g/kg) i.p. The VR1 knock-out mice (filled bar) display a significantly higher plasma insulin level 2 min after the glucose load as compared to the control mice (hatched bar). This suggests that the VR1 knock-out mice does not as readily as the control mice develop high fat diet induced impaired insulin secretion. Retention of the ability

to secrete insulin in response to glucose could partially explain the normal glucose tolerance in the high fat fed VR1 knock-out mice. This suggests that inactivating or down regulating the activity of the capsaicin receptor could be useful as novel pharmacological approach in preventing or treating impaired early insulin secretion.

EXAMPLE 2

Laboratory animals: Male (n=19) Zucker obese rats were purchased from Charles River Laboratories, U.S. The rats were transported to Denmark at the age of 6 weeks and were kept under ambient controlled conditions on a normal day light cycle (lights on at 6 am, lights off at 6 pm) at the Måløv Animal Unit at Novo Nordisk A/S, Denmark from then and until the age of 9 month of age. The rats were kept in groups of 3 rats per cage until the end of the experiment in standard cages (Eurostandard Type IV, Techniplast, Scanbur, Denmark) and were given free access to acidified (0,4 % citric acid) tap water and standard chow (Altromin, Brogaarden Aps, Denmark). The cages were supplied with wooden wool (Brogaarden, Denmark) as nesting material and the bedding material was aspen chips (Brogaarden, Denmark), changed twice per week as was the bottles of acidified water.

Oral glucose tolerance test (OGTT) and glucose stimulated insulin secretion

At 6 month of age, an OGTT was performed shortly after administering a capsaicin receptor antagonist (BCTC) orally. The rats were fasted for 18 hours prior to the OGTT. Fasting blood glucose and plasma insulin was determined as described below. At time -30 min, BCTC at 15 mg/kg (n=10) or vehicle (n=9) was given orally by gavage. The rats were left in the cage until time 0 where blood glucose was assessed followed by

the OGTT. In brief, glucose at a concentration of 500 mg/ml (Sygehus apotekerne, Denmark) was given orally by gavage (2 g/kg po). Blood glucose and plasma insulin was determined at time 30, 60 and 120 min after glucose. Blood samples for the determination of blood glucose and plasma insulin were obtained from the tail tip capillary of conscious, rats. Blood for the measurement of blood glucose was collected in heparinized 5 μ l capillary tubes and immediately suspended in 250 μ l EBIO buffer (EBIO, Eppendorf, Germany). Following the experiment, glucose was determined using the glucose oxidase method (EBIO, Eppendorf, Germany).

Blood for the analysis of plasma insulin was obtained by sampling app. 70 μ l blood from the tail tip capillary of conscious rats into heparinized 100 μ l capillary tubes. These tubes were spun (4000 rpm/min/ 4° C) and the 15 μ l plasma preserved and stored at - 20° C until analysis using an in house ELISA.

Figure 3 shows the blood glucose curves (a) and plasma insulin curves (b) after oral dosing of the capsaicin receptor antagonist, BCTC, to 6 month old male Zucker obese rats at time - 30min followed by an oral glucose tolerance test (OGTT) of 2 g/kg po at time 0. The vehicle treated rats (square) shows a marked increase in glucose levels (a) following the oral glucose load suggesting a delayed glucose clearance from the blood, i.e. impaired glucose tolerance. The BCTC treated rats (triangle up) shows in comparison a diminished rise in blood glucose (a) thus displaying improved oral glucose tolerance. The vehicle treated rats (square) further show a reduced glucose stimulated insulin response (b) whereas the BCTC treated rats show considerable higher levels of insulin in plasma after the oral glucose load (b). This suggests that the improvement of oral glucose tolerance in Zucker rats after the treatment with the capsaicin receptor antagonist BCTC is

in part mediated via improvement of insulin secretion. These data therefore confirm that the capsaicin receptor is involved in impaired glucose tolerance and impaired glucose stimulated insulin secretion.

5 Down-regulation of the capsaicin receptor could thus be a pharmacological approach in the prevention and treatment of impaired glucose tolerance and its related disorders and in preventing or treating impaired early insulin secretion.

10 **Measurement of inflammatory markers in mesenteric adipose tissue**

At 9 months of age, the same rats were tested re. mesenteric inflammatory mediators. The rats were fasted for 18 hours where after they were given BCTC at 15 mg/kg (n=10) or
15 vehicle (n=9) orally by gavage. One hour after treatment, the rats were anaesthetized in isoflurane and decapitated. The mesenteric adipose tissue was quickly removed and transferred to 10x volume pre-chilled RNAlater (Sigma-Aldrich, USA) and stored at -20°C. To prevent area to area effect on gene
20 expressions patterns, 0, 5-1 g tissue was homogenized in TRIzol Reagent (1 ml/100mg tissue) (TRIzol; Invitrogen Corp.). Total RNA was extracted from 200 ml homogenate according to Qiagen protocol (Qiagen RNeasy Mini handbook, 2001). First-strand cDNA was synthesized using SuperScript III reverse
25 transcriptase and random hexamer primers as described in the manufacturer's protocol (Invitrogen Corp.). cDNA of unknown samples were diluted 1:12 in nuclease-free water (Qiagen Inc.). Samples from each cDNA pool were mixed and diluted 1:6, 1:12, 1:24, 1:48, 1:96, 1:192 and 1:384 in order to create a
30 standard curve for calculation of PCR efficiency, where only PCR efficiency of 100% ($\pm 1\%$) and R^2 between 0,99 and 1 were accepted. PCR amplification mixtures (25 μ l) contained 12,5 μ l of 2x Platinum Quantitative PCR SuperMix-UDG (Invitrogen

Corp.), 0,625 μ l of reverse primer (20 μ M), 0,625 μ l forward primers (20 μ M), 0,625 μ l Probe (10 μ M) (ProbeLibrary Exiqon A/S, Denmark) and 5 μ l diluted cDNA template. Real-time quantitative PCR was carried out using MX3000P PCR machine (Stratagene, USA) with the following cycling parameters: polymerase activation for 10 minutes at 95°C and amplification for 40 cycles of 30 seconds at 95°C and 60 seconds at 60°C. After amplification amplicons were validated during gelelectrophoreses (E-Gel, Invitrogen Corp.).

Relative gene expression of iNOS and F4/80 were determined by quantitative RT-PCR comparative Ct method (Applied Biosystems. User Bulletin #2. ABI PRISM 7700 sequence detection system, 1997) using vehicle as calibrator. To normalize expression data 36B4 were used as internal standard. For each gene intron-spanning primers were designed using the public domain primer design software from ProbeLibrary Exiqon A/S (<http://www.probelibrary.com/>). Primer and probe number were as follows: 36B4 accession nr. X15096.1 sense (5'gtgttttgacaatggcagcat 3'), antisense (5'acagacgctggccacatt 3') and probe Rat#16. iNOS acc. nr. NM012611.2 sense (5'accatggagcatcccaagta 3'), antisense (5'cagcgcataccacttcagc 3') and probe Rat#71. F4/80 acc. nr. XM236797.2 sense (5'ggacttctccaagcctatcgt 3'), antisense (5'cctctcagacttctgctttgg 3') and probe Rat#26.

Figure 4 shows the effect of BCTC on gene expression of iNOS and F4/80 in mesenteric adipose tissue of 9 month old Zucker obese rats. The BCTC treated rats (filled bar) display a significantly lower level of both iNOS (a) and F4/80 (b) 1 hour after BCTC (15 mg/kg) po. This suggests that BCTC mediates improvement of oral glucose tolerance as well as improvement of stimulated insulin release by reducing low-grade inflammation in tissue and that this is mediated by antagonising the capsaicin receptor.

This suggests that inactivating or down regulating the activity of the capsaicin receptor could be useful as novel pharmacological approach for the treatment of conditions where low-grade inflammation is associated with obesity and obesity-related disorders.

Figure 1 and Figure 2 indicate mice lacking the capsaicin receptor (VR1) do not develop impaired glucose tolerance after weeks on a high fat diet and that this is partially explained by a retained early insulin response to glucose.

Figure 3 shows that oral glucose tolerance can be improved by oral administration of a capsaicin receptor antagonist (BCTC) in otherwise glucose intolerant male obese Zucker rats and that this is associated with an improvement of insulin secretion in response to oral glucose. Figure 4 shows that local inflammation is reduced in the obese Zucker rat after BCTC, suggesting that the improvement of impaired glucose tolerance is associated with reduction of low-grade inflammation.

Inhibiting the activity of the capsaicin receptor in obesity or in obesity-related diseases and disorders thus appears promising as a new pharmacological approach.

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CLAIMS

1. A method for treating obesity in a mammal in need thereof by inactivating or down regulating the activity of the
5 capsaicin receptor, comprising: administering a therapeutically-effective amount of a direct or indirect capsaicin receptor antagonist.

2. A method according to claim 1, wherein the capsaicin
10 receptor antagonist is a direct capsaicin receptor antagonist.

3. A method according to claim 1, wherein the capsaicin
receptor antagonist is an indirect capsaicin receptor
antagonist.

15

4. A method for treating obesity-related disease or disorders in a mammal in need thereof by inactivating or down regulating the activity of the capsaicin receptor, comprising:
administering a therapeutically-effective amount of a direct
20 or indirect capsaicin receptor antagonist.

5. A method according to claim 4, wherein the capsaicin
receptor antagonist is a direct capsaicin receptor antagonist.

25 6. A method according to claim 4, wherein the capsaicin
receptor antagonist is an indirect capsaicin receptor
antagonist.

7. A method according to claim 4, wherein the obesity-
30 related disease or disorder is selected from the following:
type 1 diabetes, type 2 diabetes, impaired glucose tolerance,
cardiovascular disease, hypertension, insulin resistance,
cancer and reproductive disorders.

8. A method according to claim 7, wherein the obesity-related disease or disorder is type 2 diabetes.

5 9. A method according to claim 7, wherein the obesity related disease or disorder is type I diabetes.

10. A method according to claim 7, wherein the obesity-related disease or disorder is impaired glucose tolerance.

10

11. A method according to claim 7, wherein the obesity-related disease or disorder is cardiovascular disease.

12. A method according to claim 7, wherein the obesity-
15 related disease or disorder is hypertension.

13. A method according to claim 7, wherein the obesity-related disease or disorder is cancer.

20 14. A method according to claim 13, wherein the cancer is selected from: colon cancer, rectal cancer, colorectal cancer, pancreatic cancer, esophageal cancer, breast cancer, prostate cancer, uterine cancer, kidney cancer, endometrial cancer, gall bladder cancer, thyroid cancer, liver cancer,
25 cervical cancer, ovarian cancer, stomach cancer, non-Hodgkin's lymphoma, and multiple myeloma.

15. A method according to claim 7, wherein the obesity-related disease or disorder is reproductive disorders.

30

16. A method according to claim 15, wherein the reproductive disorder is selected from: polycystic ovarian

syndrome (PCO), infertility, and impotency or erectile dysfunction.

17. A method according to any one of claims 1-16,
5 wherein the direct or indirect capsaicin receptor antagonist is selected from the following: natural products, synthetic organic compounds, peptides, proteins, antibodies, antibody fragments, single-chain antibodies and antibody-based constructs.

10 18. A method according to any one of claims 1-17 wherein the mammal is a human.

19. A kit for treating obesity or obesity-related
15 disease or disorders in a mammal in need thereof by inactivating or down regulating the activity of the capsaicin receptor, comprising a direct or indirect capsaicin receptor antagonist.

20 20. A kit according to claim 19, wherein the mammal is a human.

21. A method according to claim 7, wherein the obesity-related disease or disorder is insulin resistance.

25 22. A method for treating obesity or obesity related diseases and disorders in a mammal in need thereof by inactivating or down regulating the activity of the capsaicin receptor, comprising: administering a therapeutically-effective amount of a direct or indirect capsaicin receptor
30 antagonist in combination with a further active agent selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents and agents for the treatment of

complications resulting from or associated with obesity or obesity related diseases or disorders.

23. A method for the treatment of conditions where low-grade
5 inflammation is associated with obesity and obesity-related disorders, comprising administering to a subject in need thereof a therapeutically-effective amount of a direct or indirect capsaicin receptor.

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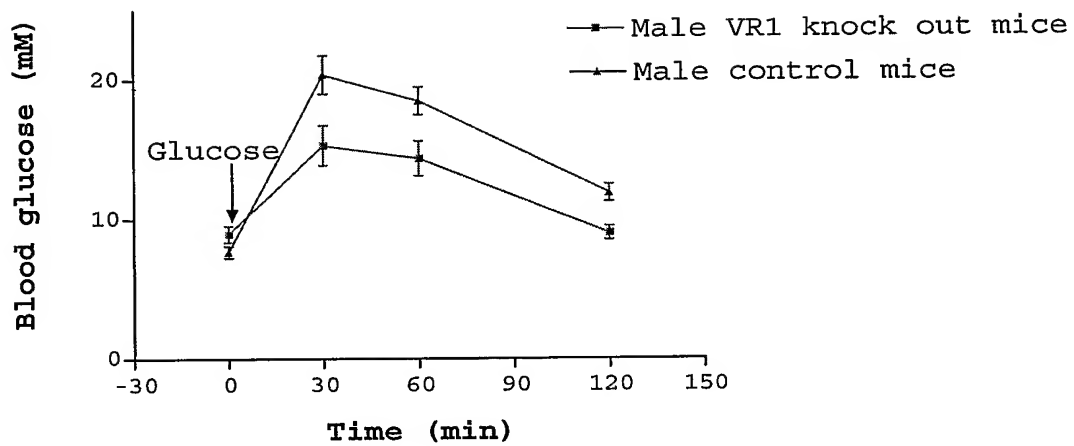


Fig. 1a

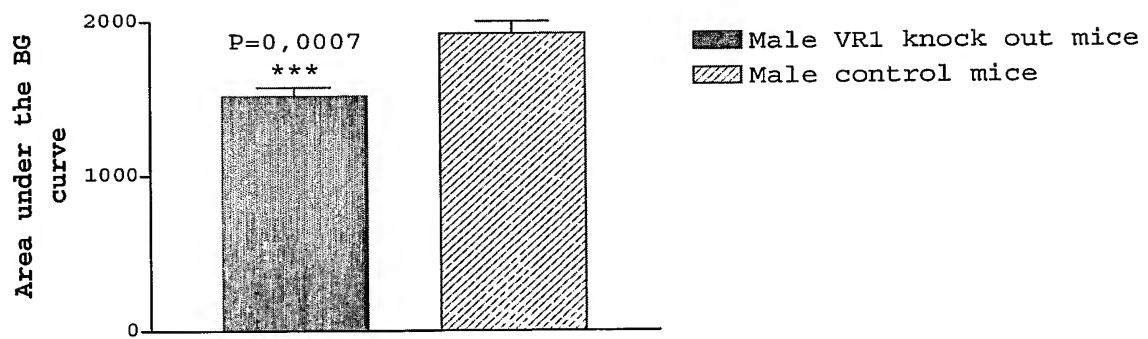


Fig. 1b

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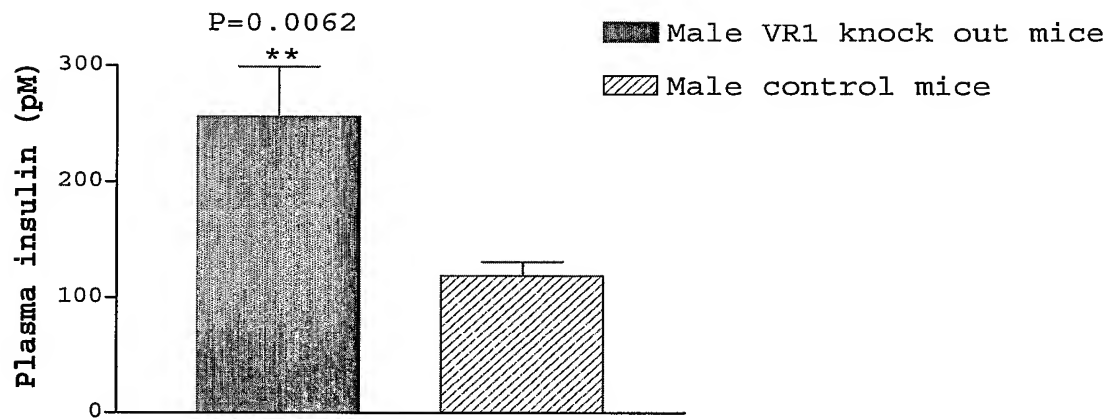


Fig. 2

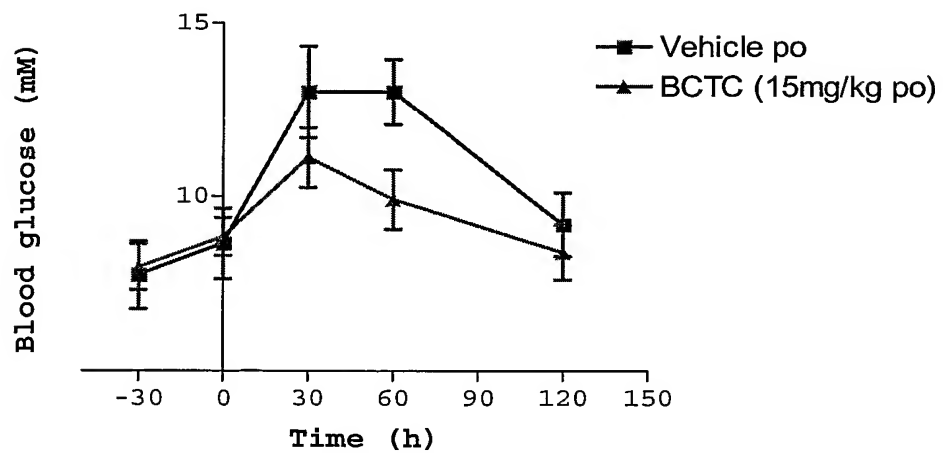


Fig. 3a

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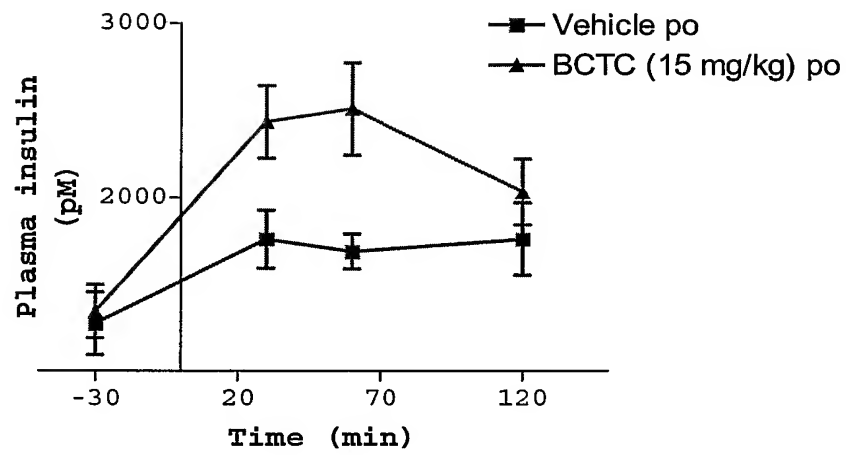


Fig. 3b

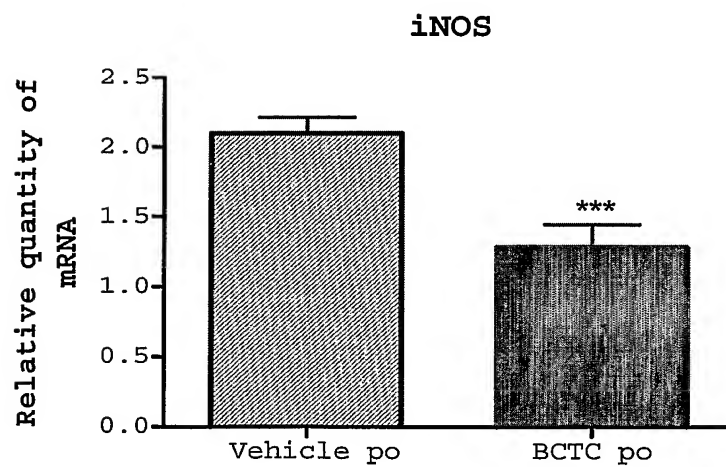
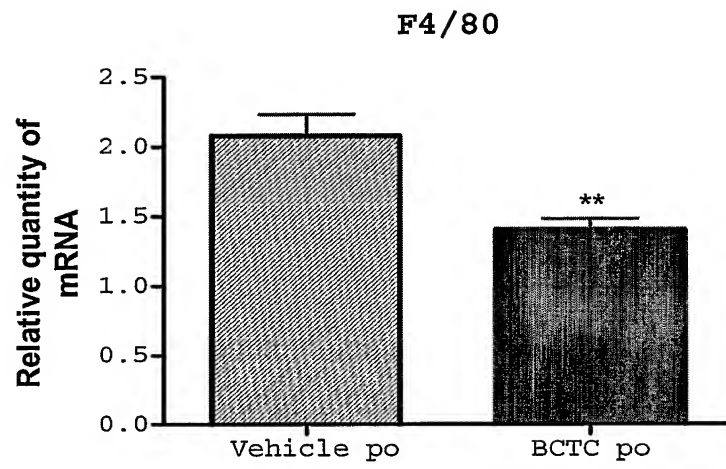


Fig. 4a

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**Fig. 4b**

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CAPSAICIN INHIBITORS FOR TREATING OBESITY AND-RELATED DISORDERS

(57) Abstract: The present invention provides a method of treating obesity and obesity-related diseases and disorders in a mammal by inhibiting the activity of the capsaicin receptor.



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INTERNATIONAL SEARCH REPORT

national application No

PCT/DK2005/000502

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/00 A61K31/497 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, PAJ, EMBASE, BIOSIS, SCISEARCH, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/066595 A (EURO-CELTIQUE S.A; KYLE, DONALD, J; SUN, QUN) 14 August 2003 (2003-08-14) page 90, lines 26-28 page 91, line 7 page 1, paragraph 2 page 113; compound 1F page 111, paragraphs 2,3 -----	4-9, 17-20, 23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Strack, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2005/000502

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-18 and 21-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national application No

PCT/DK2005/000502

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 03066595	A	14-08-2003	AU	2003212882 A1		02-09-2003
			EP	1472225 A2		03-11-2004
			JP	2005521679 T		21-07-2005
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